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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/970,651	10/05/2001	Gary L. Bowlin	VCUIP-9 V1	2603

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EXAMINER	
WEBER, JON P	

ART UNIT	PAPER NUMBER
1651	6

DATE MAILED: 04/08/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/970,651	BOWLIN ET AL.	
	Examiner	Art Unit	
	Jon P Weber, Ph.D.	1651	

-- The MAILING DATE of this communication appears n the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 January 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10 and 17-22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10 and 17-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *2,3* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Election/Restrictions – Status of the Claims

Applicant's election of Group I, claims 1-10 and 17-22 in Paper No. 5, filed 08 January 2003 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). The non-elected claims, 11-16, have been canceled.

Claim Rejections - 35 USC § 102

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 10 and 17-19 are rejected under 35 U.S.C. 102(b) as being anticipated by Tranquillo et al. (US 5,948,654).

In Tranquillo et al. (US 5,948,654), a solution of fibrin fibrils [obtained as in Torbet (1986) by combining citrated plasma containing free calcium with thrombin, or from fibrinogen/albumin mixtures combined with thrombin, a fibrin-forming solution] and cells are oriented by magnetic fields and formed into tubes using tubular molds. Smooth muscle cells are exemplified (Example 1). Any conventional cell growth or culture method may be used.

It was argued in the response of 16 May 2001 that the fibrin matrix of Torbet (1986) would dissolve too quickly and could not be used as a platform to grow cells. It is urged that Tranquillo et al. (US 5,948,654) otherwise uses purified fibrinogen like Grande et al. (US 5,906,934) and Pellegrini et al. (1999) as opposed to plasma.

The successful use by Tranquillo et al. (US 5,948,654) of the Torbet (1986) plasma based fibrin matrix to prepare tubes containing growing cells carries more weight than the

unsubstantiated assertions in the response. The distinction with respect to purified fibrinogen will be discussed below.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-10 and 17-22 rejected under 35 U.S.C. 103(a) as being unpatentable over Tranquillo et al. (US 5,948,654), Grande et al. (US 5,906,934) and Pellegrini et al. (1999) in view of Bell et al. (US 6,179,872) and Sierra (US 6,110,484).

Each of Tranquillo et al. (US 5,948,654), Grande et al. (US 5,906,934) and Pellegrini et al. (1999) disclose a fibrin matrix with cells growing therein suitable as an engineered tissue.

The teachings of Tranquillo et al. (US 5,948,654) have been discussed above. Tranquillo et al. (US 5,948,654) lack a period of time before which polymerization is not to be complete and does not teach stem cells.

In Grande et al. (US 5,906,934), a matrix containing fibrin and mesenchymal stem cells (MSCs) is constructed for defective cartilage replacement. The matrix is preferably shaped to fill the defect. When treated with dexamethasone, the stem cells differentiate into a number of mesodermal cell types. When treated inside the defect, the MSCs differentiate in such a manner as to re-create the spatial orientation of the tissue, cartilage at the surface, bone underneath.

Grande et al. (US 5,906,934) use purified fibrinogen and therefore lack plasma as the fibrinogen as instantly claimed or a period of time before which polymerization is not to be complete.

In Pellegrini et al. (1999), a solution of fibrinogen and epidermal keratinocytes containing epidermal stem cells is formed into a thin film or sheets as an artificial skin (autografts and allografts). The rate of fibrinogen polymerization is controlled by lowering the concentration of clotting agent, thrombin and calcium (page 870, column 2). Epidermal growth factor was added to facilitate cell growth in the matrix. The stem cells retained their stem cell nature during culture and after transplantation. Pellegrini et al. (1999) use purified fibrinogen and therefore lack plasma as the fibrinogen as instantly claimed or a period of time before which polymerization is not to be complete.

Bell et al. (US 6,179,872) teaches making a matt in the form of strip, sheet or tube containing living cells from a biocompatible polymer such as fibrinogen, *inter alia*. Macromolecules necessary for cell growth, morphogenesis, differentiation and tissue building may be incorporated into this matt (column 6). Epithelial, endothelial and mesenchymal cells can be plated or seeded onto the matt (column 8).

Sierra (US 6,110,484) discloses forming a biocompatible porous implant matrix with fibrinogen (column 4) for example, that dissolves slowly (more than one week) (column 3). Various growth factors and other agents may be incorporated into the matrix. The addition of antiproteases such as ϵ-amino caproic acid or aprotinin slows the degradation of the matrix when fibrin matrix is used (column 6).

A person of ordinary skill in the art at the time the invention was made would have been motivated to substitute the plasma as a "fibrin forming solution" of Tranquillo et al. (US

5,948,654) for purified fibrinogen of Grande et al. (US 5,906,934) and Pellegrini et al. (1999) to form an engineered tissue because Tranquillo et al. (US 5,948,654) as well as the instant disclosure at page 9 indicate the functional equivalence of plasma and purified fibrinogen.

Both Grande et al. (US 5,906,934) and Pellegrini et al. (1999) indicate that these fibrin matrix based engineered tissues are successfully used with stem cells. The addition of cell growth factors and stem cell differentiation factors to the engineered tissues are discussed as well. Any suitable cell may be grown in this manner using conventional cell culturing methods. Hence, it would be obvious to use cells that have been genetically modified by the many techniques known in the art. In Pellegrini et al. (1999) the allograft versions of the tissue are used during the period while autograft tissue is being grown for subsequent use. The advantages of autograft are well known in the art and include: lack of rejection and freedom from foreign contaminant viruses, for example.

Pellegrini et al. (1999) do not specifically indicate the desire for clot formation of more than ten seconds, however, Pellegrini et al. (1999) do clearly indicate that they needed to lengthen the clotting time by reducing the concentration of thrombin and calcium so as to obtain a matrix that could be formed into a suitable cell-containing film. The manufacturer's instructions gave a solution which clotted too rapidly. At page 869, column 2, complete fibrin substrate polymerization was obtained in 10-15 minutes at room temperature. This implies that clot formation took longer than ten seconds by their method.

The addition of antiproteases is expected to decrease the biodegradation rate as disclosed by Sierra (US 6,110,484)

Hence, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to substitute the plasma of Tranquillo et al. (US 5,948,654) as a fibrin forming solution for the purified fibrinongen of Grande et al. (US 5,906,934) and Pellegrini et al. (1999) and to control the clotting time so as to obtain a suitable engineered tissue.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon P Weber, Ph.D. whose telephone number is 703-308-4015. The examiner can normally be reached on daily, off 1st Fri, 9/5/4.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Wityshyn can be reached on 703-308-4743. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Jon P Weber, Ph.D.
Primary Examiner
Art Unit 1651

JPW
March 31, 2003